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Elyssa B. Margolis, Ph.D.

Curriculum Vitae

Position

Associate Professor in Residence
Endowed Chair in Genetics of Addiction
Department of Neurology
School of Medicine

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EDUCATION

1996 - 1999	Harvey Mudd College	B.S.	Major: Engineering Minor: Psychology
1999 - 2003	UCSF/UC Berkeley Joint Graduate Group in Bioengineering	Ph.D.	Bioengineering Major: Neuroscience Minors: Transport, Drug Design
2004 - 2006	UCSF/Ernest Gallo Clinic & Research Center	Post-doctoral fellow	

PRINCIPAL POSITIONS HELD

2007 - 2009	Ernest Gallo Clinic & Research Center	Assistant Research Scientist	
2010 - 2016	University of California, San Francisco	Assistant Adjunct Professor	Neurology
2016 - 2019	University of California, San Francisco	Associate Adjunct Professor	Neurology
2019 - present	University of California, San Francisco	Associate Professor in Residence	Neurology

OTHER POSITIONS HELD CONCURRENTLY

2010 - 2013	Ernest Gallo Clinic & Research Center	Associate Investigator

HONORS AND AWARDS

2020	Selected for the "Academic Leadership for Women in Engineering" Program	Society of Women Engineers
2018	Young Pioneer	Winter Conference on Brain Research
2011	Semi-finalist in the Berkeley Business Plan Competition	Hass School of Business, UC Berkeley
2009	Poster Award	International Narcotics Researchers' Conference
2003	Winner of the BioBiz VC Competition	Women's Technology Cluster (now Astia)
2002	Finalist in the Berkeley Business Plan Competition	Hass School of Business, UC Berkeley
1999	Departmental Honors, Engineering Department	Harvey Mudd College
1999	Graduation with Distinction	Harvey Mudd College

Areas of Interest/Keywords

Neuroscience, synaptic physiology, pharmacology, G protein coupled receptors, neurocircuitry, neuroanatomy, behavioral pharmacology, addiction, alcoholism, pain, electrophysiology, systems neuroscience, neuropeptides, neuromodulators, opioid peptides, opioid receptors, GABA-A receptor

Professional Activities

PROFESSIONAL ORGANIZATIONS: MEMBERSHIPS AND CERTIFICATIONS

2001 - present	Society for Neuroscience
1995 - present	Society of Women Engineers
2000	Board for Professional Engineers and Land Surveyors, state of CA, EIT Certification

SERVICE TO PROFESSIONAL ORGANIZATIONS

2020-present	Program Chair	Kappa Therapeutics Conference
2010, 2020	Grant Reviewer	ZonMw
2019	Program Committee	Kappa Therapeutics Conference
2018	Program Committee	International Narcotics Researchers' Conference
2018 - present	Board of Directors	Winter Conference on Brain Research

2017 - present	Travel Fellow Committee	Winter Conference on Brain Research
2017 - present	Travel Fellow Mentor	Winter Conference on Brain Research
2017	Grant Reviewer	European Commission
2015	Grant Reviewer	Institute for Mental Health Research
2015	Grant Reviewer	Arizona's Institute for Mental Health Research
2014	Session Discussant at Annual Meeting	International Narcotics Researchers' Conference
2014	Grant Reviewer	Parkinson's UK
2011 - 2012	Annual Meeting Organizing Committee Member	International Narcotics Researchers' Conference
1997 - 1999	President of Harvey Mudd College Section	Society of Women Engineers
1996 - 1997	Secretary of Harvey Mudd College Section	Society of Women Engineers

SERVICE TO PROFESSIONAL PUBLICATIONS

Ad hoc referee for:

- Journal of Neuroscience
- European Journal of Neuroscience
- Neuroscience Letters
- Life Sciences
- Neuropharmacology
- British Journal of Pharmacology
- PLoS One
- Progress in Neuropsychopharmacology & Biological Psychiatry
- Journal of Chemical Neuroanatomy
- Current Biology
- Physiological Research
- Journal of Psychopharmacology
- Frontiers Psychiatry
- Frontiers Neuroscience
- Frontiers Pharmacology
- Pain
- Nature Communications
- Nature Neuroscience
- eNeuro
- ACER
- Brain Research
- Science
- Neuropharmacology
- Scientific Reports
- Journal of Clinical Investigation
- Addiction Neuroscience
- eLife

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2021	NIH: SEP ZRG1 IFCN-J study section	Grant Reviewer
2021	NIH: MNPS study section	Grant Reviewer
2020	NIH: ZRG1 MDCN-R study section	Grant Reviewer
2019	NIH: NMB study section	Grant Reviewer

2018	NIH: Behavioral Neuroscience F02A-K Panel	Grant Reviewer
2017	NIH: ETTN-D study section	Grant Reviewer
2017	VA: NURA study section	Grant Reviewer
2015	NIH: MNPS study section	Grant Reviewer
2015	Institute for Mental Health Research	Grant Reviewer
2013	NIDA CEBRA Program	Grant Reviewer

CONSULTANTSHIP TO THE PHARMACEUTICAL INDUSTRY

Epiodyne, Inc. (2017 - 2019)

University and Public Service

UNIVERSITY UC SYSTEMWIDE SERVICE

2020 - present	Pain and Addiction Research Center (PARC), UCSF	• Retreat Co-chair, • Co-lead of Buprenorphine working group, • Seminar Steering Committee
2019	Pain and Addiction Research Retreat, UCSF	Organizer
2015 - present	Wheeler Center for the Neurobiology of Addiction	Scientific Program Director
2003	Bioengineering Research Forum at UCB/UCSF	Organizer
2003	Bioengineering Association of Students at UCB/UCSF	Graduate Representative
2001 - 2002	UCSF/UC Berkeley Joint Graduate Group of Bioengineering	Qualifying Exam Advisor
2000 - 2001	UCSF/UC Berkeley Joint Graduate Group in Bioengineering	Head Peer Advisor
1999 - 2000	UCB/UCSF bioengineering graduate students	Outdoor Event Coordinator

During the pandemic, most of my work organizing for the Wheeler Center and AARG have been paused. However, I have been active in the newly formed UCSF Pain and Addiction Research Center (PARC). This work has included choosing external seminar speakers and moderating these events and co-leading the newly formed working group on Buprenorphine. I suggested that we build the group around interest in Buprenorphine because in the clinic it is an effective replacement treatment for opioids but also prevents the respiratory depression that leads to opioid induced mortality. The pharmacological properties of the drug are poorly understood, and discoveries may lead to improved

therapeutic design both for opioid use disorder as well as pain. On the clinical side, Buprenorphine is underutilized due to prescription hesitancy related to a lack of adequate information and education of clinicians. For those clinicians that do use it in their practice, anecdotal observations will help this group to identify critical human as well as preclinical studies to better understand what confers the advantageous drug profile to Buprenorphine. Deliverables we are working towards are increased exchange of information between clinicians and bench scientists, education of clinicians, outreach to clinicians who treat underserved minority groups, bench science pilot collaborations, and NIH center grant applications.

As part of my role as Scientific Program Director of the Wheeler Center for the Neurobiology of Addiction, I organize the annual Wheeler Center Retreat. The Wheeler Center, an association of UCSF professors, has brought together scientists in genetics and in cell, molecular and systems neuroscience to explore and identify nervous system changes that lead to addiction; holding a retreat is an opportunity for scientists in these various fields to come together to brainstorm for new hypotheses and experiments, as well as to foster future collaborations across the UCSF and greater Bay Area community. For this day long retreat, members of the community from UC Berkeley and Stanford also join us for an intense, exciting day of sharing new research and ideas, focusing in on specific topics for in depth discussions.

In December of 2019, we hosted a joint retreat with the newly formed UCSF Pain and Addiction Research Center. This 1 day event was held in the Helen Diller Building on the Mission Bay Campus, with over 80 UCSF registrants representing basic science and clinical researchers.

In 2017 the topic of the retreat was opioids, and our special guest speaker is Dr. Frank Porreca (U of A).

In 2016 our retreat topic was the prefrontal cortex, and our special guest speaker was Dr. Jeremy Seamans (UBC).

In 2015 I organized the retreat on dopamine, and our guest speaker was the internationally respected Dr. David Sulzer, PhD, of Columbia University.

In 2018-2019, I organized an annual UCSF Addiction Research Poster Sessions, afternoon events held at the Mission Bay Campus.

Feedback from attendees indicates these events are not only enjoyed by all and informative, they also have generated new research directions and collaborations.

UNIVERSITY UCSF SERVICE

2020 - 2021	Qualifying Exam Committee (Leah Vinson, Neuroscience program)	Committee Member
2019	Qualifying Exam Committee (Chase Webb, PSPG program)	Committee Member
2018 - 2019	Alcohol and Addiction Research Group	Seminar Program Organizer

PUBLIC SERVICE

2001 - 2009	Berkeley Art Center	Web Mistress

2000 - 2002	Empowering Women of Color Conference	Organizing Committee Member, Web Mistress
2002 - 2002	Mentoring in Science, Engineering & Technology Program, The United Department of Labor Women's Bureau	Mentor

Teaching and Mentoring

FORMAL TEACHING

Year	Class Name	Role	Hours	# Students
2017 - present	Mind, Brain, Behavior	Neurophysiology Discussion Leader	4	20
2015 - present	SDM BMS 118 Organ Systems and Human Pathophysiology, Part 1	Neuroscience of Addiction Lecturer	2	150
2014	NS219 - Topics in Basic or Translational Neuroscience	Lectures on the Neurophysiology of Addiction	8	6

INFORMAL TEACHING

2011 - 2012	Led and participated in Gallo Center journal club for postdocs and graduate students sponsored by the ACTG Center Grant

MENTORING

Predoctoral Students Supervised or Mentored

Dates	Name	Program or School	Role	Current Position
2020 - 2021	Aaron Berson	UCSF volunteer and lab intern	Supervisor	Lab intern
2020 - 2021	Albert Lee	UCSF volunteer and lab intern	Supervisor	Lab intern
2018 - 2021	Joshua Bastacky	UCSF Summer Intern and Reed College Senior Thesis Program	Supervisor and Mentor	Research Asst., UCSF
2018 - 2018	David Dunn	UCSF Summer Intern	Supervisor	Reed College Graduate
2016 - 2017	Vivien Lu	UCSF volunteer and lab intern	Supervisor	Medical Student
2017 - 2017	Samuel Chia	UCSF volunteer and lab intern	Supervisor	

Dates	Name	Program or School	Role	Current Position
2015 - 2018	Jocelyn Breton	UC Berkeley Neuroscience Graduate Program	Mentor	UC Berkeley PhD completed
2014 - 2017	Joseph Driscoll	UC Berkeley Neuroscience Graduate Program	Mentor	Data scientist at nom nom now
2014 - 2014	Rose Larios	UCSF Neuroscience Graduate Program	Rotation mentor	UCSF Neuroscience Graduate Student
2010 - 2013	Allison Coker	UCSF Neuroscience Graduate Program	Mentor	Clinical Research Analyst & Program Manager at UCSF
2012 - 2014	Bryan Fowler	UCSF Lab Intern	Supervisor	UT Southwestern Graduate Student
2012 - 2016	Ryan Young	UCSF Lab Intern	Supervisor	Physical Therapy Student
2012 - 2012	Kelly Pagano	Gallo Center Volunteer	Supervisor	Clinical Laboratory Scientist at Invitae
2012 - 2012	Elayne Viera Dias	Summer Intern from Lab. de Neurobiologia da Dor Depto. de Anatomia, Biologia Celular e Fisiologia, Instituto de Biologia, Unicamp	Supervisor	University of Campinas Postdoctoral Fellow
2011 - 2011	Patricia Himmels	Gallo Center Intern	Supervisor	Scientist, Genentech
2010 - 2010	Anne-Iris Lemaitre	Gallo Center Intern	Supervisor	Centre Hospitalier Universitaire de Bordeaux Intern
2008 - 2009	Harry Ching	Gallo Center Intern	Supervisor	UNLV School of Medicine Resident
2006 - 2008	Brian Toy	Gallo Center Intern	Supervisor	USC Clinical Instructor

Postdoctoral Fellows and Residents Directly Supervised or Mentored

Dates	Name	Role	Current Position
2021 - present	Elayne Vieira Dias	Supervisor	
2021 - present	Philip Lambeth	Supervisor	

Dates	Name	Role	Current Position
2020 - present	Thomas Cirino	Supervisor	
2014 - 2020	Maggie Waung	Mentor and Co-Supervisor	Neurology Adj Asst Professor
2017 - 2019	Joseph Driscoll	Supervisor	Data scientist nom nom now
2013 - 2016	Annabelle Charbit-Bergenfeld	Supervisor	UCSF Laboratory Manager
2008 - 2012	Tom Hnasko	Mentor	Assistant Professor of Neuroscience at University of California, San Diego
2006 - 2007	Jonathan Kalkstein	Mentor	Psychiatrist, Contra Costa County Regional Medical Center

Invited Lectures

2022	Winter Conference on Brain Research	Panel Speaker, Session Chair
2019	Washington University, St. Louis, MO	Seminar Speaker
2019	Society for Neuroscience Meeting, Chicago, IL	Minisymposium Co-Chair and Speaker
2019	Therapeutic Potential of Kappa Opioids Conference, Seattle, WA	Speaker, Session Chair
2019	University of Arizona, Phoenix	Seminar Speaker
2019	Winter Conference on Brain Research	Panel Speaker, Session Chair
2018	California Society for Addiction Medicine State of the Art Conference, San Francisco, CA	Speaker
2018	Research Society on Alcohol Conference, San Diego, CA	Panel Speaker
2018	International Narcotics Researchers Conference, San Diego, CA	Panel Speaker, Session Chair
2018	Pain Mechanisms and Therapeutics Conference, Taormina, Sicily	Panel Speaker
2018	Pain Research Forum Https://www.painresearchforum.org/forums/webinar/90976-webinar-kappa-opioid-antagonists-migraine-and-pain	Invited Discussant for Webinar
2018	Northwestern University	Seminar Speaker

2018	Winter Conference on Brain Research	Special Junior Pioneer Speaker, Panel Speaker
2017	Gordon Conference on Catecholamines, Sunday River, ME	Panel Speaker
2017	Therapeutic Potential of Kappa Opioids Conference, Philadelphia, PA	Speaker
2017	Winter Conference on Brain Research	2 Panel Talks, Session Chair
2016	Dopamine 2016 Meeting, Vienna, Austria	Panel Speaker
2016	Columbia University, New York, NY	Seminar Speaker
2016	PATH FoundationNew York, NY	Panel Speaker
2016	LSU Health Sciences Center, New Orleans, LA	Seminar Speaker
2015	Drexel University, Philadelphia, PA	Seminar Speaker
2015	International Narcotics Researchers Conference, Phoenix, AZ	Speaker
2015	Ichan School of Medicine at Mt. Sinai, New York	Seminar Speaker
2015	Winter Conference on Brain Research	Panel Speaker, Session Chair
2014	International Narcotics Researchers Conference, Montreal, Canada	Panel Discussion Leader
2014	Monitoring Molecules in Neuroscience, Los Angeles, CA	Panel Speaker, Session Chair
2014	Winter Conference on Brain Research	Panel Speaker
2013	Kappa Therapeutics Meeting, Boston, MA	Speaker
2013	Gordon Conference on Catecholamines, Mt. Snow, VT	Panel Speaker
2013	Society for Neuroscience Meeting, San Diego, CA	Panel Speaker
2013	SRI International, Menlo Park, CA	Seminar Speaker
2013	University of North Carolina, Chapel Hill, NC	Seminar Speaker
2012	Plasticity in the Basal Ganglia: Dopamine and Beyond, Beijing, China	Panel Speaker
2012	Torrey Pines Institute for Molecular Studies, Port St. Lucie, FL	Distinguished Speaker
2012	International Narcotics Researchers Conference, Kansas Vity, MO	Panel Speaker, Session Chair

2011	International Narcotics Researchers Conference, Hollywood, FL	Panel Speaker
2009	Winter Conference on Brain Research, Copper Mountain, CO	Panel Speaker
2008	International Narcotics Researchers Conference, Charleston, SC	Panel Speaker
2007	Dopamine 50 Years Congress, Sweden	Panel Speaker
2007	Workshop on Neurosystems, Stanford University, CA	Speaker
2007	Albert Einstein College of Medicine of Yeshiva University, New York, NY	Seminar Speaker
2004	National Institute of Drug Abuse, Baltimore, MD	Seminar Speaker

Research and Creative Activities

RESEARCH AWARDS

Current

Painless Research Foundation (PI)	1/01/2022 - 12/31/2022
Opioid responsive circuits in the lateral habenula	$80,000 direct gift
R21DA051208 (PI)	03/01/2021 – 02/28/2023
NIDA	$225,000 direct/yr direct/yr1
Resolving differences between clinical opioids at single neurons	
R01AA026609 (PI)	09/10/2018 – 06/30/2023
NIAAA	$225,000 direct/yr direct/yr1
Understanding endogenous opioid drive of alcohol consumption	
R01DA042025 (PI)	09/01/17 - 06/30/22
NIDA	$225,000 direct/yr direct/yr1
The role of the VTA-lateral habenula circuit in opioid mediated behaviors	

Past

PI, Sponsored Research Agreement	07/26/2016 - 07/31/2021
BlackThorn Therapeutics, Inc.	$237,000 direct total

Characterizing Novel Kappa Opioid Receptor Antagonists and Orphanin Like Receptor Antagonists Using *ex vivo* Electrophysiological Recordings	
R01 DA030529 (PI)	01/01/11 - 11/30/15
NIDA	$225,000 direct/yr direct/yr1
Heterogeneity of Ventral Tegmental Area Neurons and Opioid Reward	
(PI)	11/01/15 - 10/31/16
Wheeler Center for the Neurobiology of Addiction	$60,000 total direct/yr1
Ventral tegmental area extrasynaptic GABAA receptor role in ethanol reward	
5P50AA017072-08 (PI of subaward)	11/01/14 - 10/31/15
NIAAA/Wheeler Center for the Neurobiology of Addiction	$50,000 direct/yr direct/yr1
Ventral tegmental area extrasynaptic GABAA receptor role in ethanol reward	
5 P50 AA017072-04 (PI of subaward)	05/01/10 - 04/30/12
NIAAA, Alcohol Center for Translational Genetics (ACTG) Center Grant	$50,000 direct/yr 1 direct/yr1
VTA Mechanisms involved in stress-induced ethanol consumption	$100,000 entire period total
(PI)	
Wheeler Center for the Neurobiology of Addiction	2001
Graduate Student Research Grant	

PEER REVIEWED PUBLICATIONS

1. **Margolis EB**, Hjelmstad GO, Bonci A, Fields HL. Kappa-opioid agonists directly inhibit midbrain dopaminergic neurons. J Neurosci. 2003 Nov 5; 23(31):9981-6. PMID: 14602811 "This week in the Journal" feature Cited 292 times (as of March, 10, 2021)

2. **Margolis EB**, Hjelmstad GO, Bonci A, Fields HL. Both kappa and mu opioid agonists inhibit glutamatergic input to ventral tegmental area neurons. J Neurophysiol. 2005 Jun; 93(6):3086-93. PMID: 15615834 Topic of "Editorial Focus" in this issue. Cited 81 times (as of March, 10, 2021)

3. **Margolis EB**, Lock H, Chefer VI, Shippenberg TS, Hjelmstad GO, Fields HL. Kappa opioids selectively control dopaminergic neurons projecting to the prefrontal cortex. Proc Natl Acad Sci U S A. 2006 Feb 21; 103(8):2938-42. PMID: 16477003 Cited 315 times (as of March, 10, 2021)

4. **Margolis EB**, Lock H, Hjelmstad GO, Fields HL. The ventral tegmental area revisited: is there an electrophysiological marker for dopaminergic neurons? J Physiol. 2006 Dec 15; 577(Pt 3):907-24. PMID: 16959856 Cited 547 times (as of March, 10, 2021)

5. **Margolis EB**, Mitchell JM, Ishikawa J, Hjelmstad GO, Fields HL. Midbrain dopamine neurons: projection target determines action potential duration and dopamine D(2) receptor inhibition. J Neurosci. 2008 Sep 3; 28(36):8908-13. PMID: 18768684 Cited 255 times (as of March, 10, 2021)

6. **Margolis EB**, Fields HL, Hjelmstad GO, Mitchell JM. Delta-opioid receptor expression in the ventral tegmental area protects against elevated alcohol consumption. J Neurosci. 2008 Nov 26; 28(48):12672-81. PMID: 19036960 Cited 95 times (as of March, 10, 2021)

7. Dobi A, **Margolis EB**, Wang HL, Harvey BK, Morales M. Glutamatergic and nonglutamatergic neurons of the ventral tegmental area establish local synaptic contacts with dopaminergic and nondopaminergic neurons. J Neurosci. 2010 Jan 6; 30(1):218-29. PMID: 20053904. Cited 205 times (as of March, 10, 2021)

8. Xia YF, **Margolis EB**, Hjelmstad GO. Substance P inhibits GABAB receptor signalling in the ventral tegmental area. J Physiol. 2010 May 1; 588(Pt 9):1541-9. PMID: 20231139. Cited 18 times (as of March, 10, 2021)

9. **Margolis EB**, Coker AR, Driscoll JR, Lemaître AI, Fields HL. Reliability in the identification of midbrain dopamine neurons. PLoS One. 2010; 5(12):e15222. PMID: 21151605. Cited 73 times (as of March, 10, 2021)

10. Xia Y, Driscoll JR, Wilbrecht L, **Margolis EB**, Fields HL, Hjelmstad GO. Nucleus accumbens medium spiny neurons target non-dopaminergic neurons in the ventral tegmental area. J Neurosci. 2011 May 25; 31(21):7811-6. PMID: 21613494. Cited 224 times (as of March, 10, 2021)

11. **Margolis EB**, Mitchell JM, Hjelmstad GO, Fields HL. A novel opioid receptor-mediated enhancement of GABAA receptor function induced by stress in ventral tegmental area neurons. J Physiol. 2011 Sep 1; 589(Pt 17):4229-42. PMID: 21690191. Cited 25 times (as of March, 10, 2021)

12. Mitchell JM, **Margolis EB**, Coker AR, Fields HL. Alcohol self-administration, anxiety, and cortisol levels predict changes in delta opioid receptor function in the ventral tegmental area. Behav Neurosci. 2012 Aug; 126(4):515-22. PMID: 22708955. Cited 13 times (as of March, 10, 2021)

13. **Margolis EB**, Toy B, Himmels P, Morales M, Fields HL. Identification of rat ventral tegmental area GABAergic neurons. PLoS One. 2012; 7(7):e42365. PMID: 22860119. Cited 168 times, among the 10% most cited PLoS One articles (as of March, 10, 2021).

14. Hjelmstad GO, Xia Y, **Margolis EB**, Fields HL. Opioid modulation of ventral pallidal afferents to ventral tegmental area neurons. J Neurosci. 2013 Apr 10; 33(15):6454-9. PMID: 23575843 Cited 86 times (as of March, 10, 2021)

15. Mitchell JM, **Margolis EB**, Coker AR, Allen DC, Fields HL. Intra-VTA Deltorphin, But Not DPDPE, Induces Place Preference in Ethanol-Drinking Rats: Distinct DOR-1 and DOR-2 Mechanisms Control

Ethanol Consumption and Reward. Alcohol Clin Exp Res. 2014 Jan; 38(1):195-203. PMID: 24033469. Cited 25 times (as of March, 10, 2021)

16. Berthet A, **Margolis EB**, Zhang J, Hsieh I, Zhang J, Hnasko TS, Ahmad J, Edwards RH, Sesaki H, Huang EJ, Nakamura K. Loss of mitochondrial fission depletes axonal mitochondria in midbrain dopamine neurons. J Neurosci. 2014 Oct 22; 34(43):14304-17. PMID: 25339743. Cited 132 times (as of March, 10, 2021)

17. **Margolis EB**, Hjelmstad GO, Fujita W, Fields HL. Direct Bidirectional μ-Opioid Control of Midbrain Dopamine Neurons. J Neurosci. 2014 Oct 29; 34(44):14707-16. PMID: 25355223. Cited 71 times (as of March, 10, 2021)

18. Gomes I, Bobeck EN, **Margolis EB**, Gupta A, Sierra S, Fakira AK, Fujita W, Müller TD, Müller A, Tschöp MH, Kleinau G, Fricker LD, Devi LA. Identification of GPR83 as the receptor for the neuroendocrine peptide PEN. Sci Signal. 2016; 9(425):ra43. PMID: 27117253. PMCID: PMC5147544 Cited 41 times (as of March, 10, 2021)

19. Avegno EM, Salling MC, Borgkvist A, Mrejeru A, Whitebirch AC, **Margolis EB**, Sulzer D, Harrison NL. Voluntary adolescent drinking enhances excitation by low levels of alcohol in a subset of dopaminergic neurons in the ventral tegmental area. Neuropharmacology. 2016 Nov; 110(Pt A):386-95. PMID: 27475082 Cited 23 times (as of March, 10, 2021)

20. **Margolis EB**, Fields HL. Mu Opioid Receptor Actions in the Lateral Habenula. PLoS One. 2016; 11(7):e0159097. PMID: 27427945. PMCID: PMC4948872 Cited 34 times, viewed 2923 times (as of March, 10, 2021)

21. **Margolis EB**, Fujita W, Devi LA, Fields HL. Two delta opioid receptor subtypes are functional in single ventral tegmental area neurons and can interact with the mu opioid receptor. Neuropharmacology. 2017 Sept; 123: 420-32. Cited 24 times (as of March, 10, 2021)

22. Saunders BT, RIchard JM, **Margolis EB**, Janak PH. Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. 2018 Nature Neurosci 21(8) 1072-83. Cited 125 times (as of March, 10, 2021)

23. Breton JM, Charbit AR, Snyder BJ, Fong PTK, Dias EV, Himmels P, Lock H, **Margolis EB**. Relative contributions and mapping of ventral tegmental area dopamine and GABA neurons by projection target in rat. J Comp Neurol. 2019 527(5):916-41. Cited 35 times (as of March, 10, 2021) Altmetric score 64

24. Waung MW, **Margolis EB**, Charbit AR, Fields HL. A midbrain circuit that mediates headache aversiveness in rats. Cell Rep. 2019 28(11):2739-2747. Cited 5 times (as of March, 10, 2021)

25. Gomes I, Sierra S, Lueptow L, Gupta A, Gouty S, **Margolis EB**, Cox BM, Devi LA. Biased signaling by endogenous opioid peptides. Proc Natl Acad Sci U S A. 2020 May 11. Cited 17 times (as of March, 10, 2021)

26. Driscoll JR, Wallace TL, Mansourian KA, Martin WJ, **Margolis EB.** Differential modulation of ventral tegmental area circuits by the nociceptin/orphanin FQ system. eNeuro 2020.0376-19.2020 Cited 3 times (as of March, 10, 2021).

27. **Margolis EB**, Wallace TL, Van Orden LJ, Martin WJ. Differential effects of novel kappa opioid receptor antagonists on dopamine neurons using acute brain slice electrophysiology. PLoS One. 2020; Dec 29;15(12):e0232864. PMCID: PMC7771853 Cited 1 time (as of March, 10, 2021)

28. Miranda-Barrientos J, Chambers I, Mongia S, Liu B, Wang HL, Mateo-Semidey GE, **Margolis EB**, Zhang S, Morales M. Ventral tegmental area GABA, glutamate, and glutamate-GABA neurons are heterogenous in their electrophysiological and pharmacological properties. Eur J Neurosci. 2021 Feb 22.

29. Nuthikattu N, Jilakara R, Nelson MNF, Asher WB, Eans SO, Wilson LL, Chintala SM, Filizola M, van Rijn RM, **Margolis EB**, Roth BL, McLaughlin JP, Che T, Sames D, Javitch JA, Majumdar S. A voel mitragynine analog with low-efficacy mu opioid receptor agonism displays antinociception with attenuated adverse effects. J Med Chem 2021 Sept 23; 64(18):13873 - 13892.

30. Waung MW, Maanum KA, Cirino TJ, Driscoll JR, O'Brien C, Bryant S, Mansourian KA, Morales M, Barker DJ, **Margolis EB.** A diencephalic circuit in rats for opioid analgesia but not positive reinforcement. Nat Commun. 2022 Feb 9; 13(1):764.

PUBLISHED REVIEW ARTICLES

1. Fields HL, Hjelmstad GO, **Margolis EB**, Nicola SM. Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement Annu Rev Neurosci 2007 30:289-316. Cited 581 times (as of March, 10, 2021)

2. Volman SF, Lammel S, **Margolis EB**, Kim Y, Richard JM, Roitman MF, Lobo MK. New Insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. J Neurosci 2013 33(45):17569-76 Cited 144 times (as of March, 10, 2021)

3. Fields HL, **Margolis EB**. Understanding opioid reward. Trends in Neurosciences 2015 38(4):217-225. Cited 257 times (as of March, 10, 2021)

4. Morales M, **Margolis EB**. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat Rev Neurosci. 2017 Jan 05. PMID: 28053327 Cited 458 times (as of March, 10, 2021).

5. **Margolis EB**, Karkhanis AN. Dopaminergic cellular and circuit contributions to kappa opioid receptor mediated aversion. Neurochem Int. 2019 Oct; 129. Cited 16 times (as of March, 10, 2021)

6. Fricker LD, **Margolis E**, Gomes I, Devi LA. Five decades of research on opioid peptides: Current knowledge and unanswered questions. Mol Pharmacol. 2020 Jun 02. Cited 13 times (as of March, 10, 2021)

PATENTS ISSUED

METHODS OF USING SELECTIVE DELTA OPIOID RECEPTOR-1 AGONISTS, DELTA OPIOID RECEPTOR-2 ANTAGONISTS, AND/OR MU OPIOID RECEPTOR ANTAGONISTS FOR TREATMENT OF ADDICTIVE DISEASES

Research Program

My research comprises investigations into the circuits and GPCR pharmacologies that dictate positive reinforcement and pain relief. At the center of the circuits we study are the ventral tegmental area (VTA) and the lateral habenula (LHb). The VTA is the source of dopamine in the reward circuitry of the brain. One aspect of the work is to determine the physiological and behavioral consequences of opioid receptor activation in this part of the limbic circuit, and to determine how these effects sort with the projection target of the individual VTA neurons. We have found that these effects differ depending on whether the VTA neurons are dopaminergic or not, and whether they project to the nucleus accumbens, amygdala, prelimbic cortex, infralimbic cortex, or lateral habenula (LHb). We are investigating how they change in disease states and following drugs of abuse and/or stress, with the goal of identifying a target for a treatment for alcoholism and substance use disorder. We also perform pharmacological *ex vivo* studies to probe the heterogeneity of VTA neurons in conjunction with detailed anatomical and morphological analyses of their circuitry. The VTA neurons are rich in neuropeptide receptors, especially opioid receptors, enabling us to utilize acute brain slices to differentiate GPCR pharmacologies that have been difficult to detect in heterologous systems. This method of testing compound pharmacology in real brain tissue at the single neuron, physiological level, gives us the opportunity to more accurately predict *in vivo* behavioral activity than heterologous systems. To complement these studies of the reinforcement system, we are also investigating how the LHb is activated and modulated in pain states. The LHb received input from the VTA, and projects back to the VTA, both directly and via circuit connections. We have found that opioid receptor activation in the LHb inhibits neural activity and generates pain relief, and that the key excitatory innervation arises from the lateral preoptic area of the hypothalamus. We utilize microscopy, electrophysiology, behavioral pharmacology, anatomical tracing, optogenetic, electrochemistry, and fiber photometry techniques to study these systems. Together, this ongoing research informs our understanding of the normal and compromised function of the motivational circuits through the VTA and LHb, with the goal of identifying new molecular targets for therapeutically modulating these circuits.

NIH BIOSKETCH CONTRIBUTIONS TO SCIENCE

1. The heterogeneity of the VTA: Until very recently, most in vivo and ex vivo electrophysiological experiments assumed that midbrain dopamine neurons were homogeneous in their firing patterns, electrophysiological properties, and pharmacological responses. This began to change after our 2006 report that when systematically sampled from throughout the VTA and identified with immunocytochemistry, not only were the properties and pharmacological responses of confirmed dopamine neurons heterogeneous, but they were indistinguishable from adjacent non-dopamine neurons [1]. Because of the challenge to existing canon, other researchers claimed that TH immunoreactivity "washed out" during whole cell recordings (Zhang et al., 2010); we rigorously tested this, publishing in 2010 that when we followed their methods, recording with a high Cl- concentration internal solution, we replicated the decrease in TH immunoreactivity [2]. However, we also demonstrated that recording with the K gluconate based solution that we use for most recordings does not interfere with TH immunoreactivity [2]. We pursued this issue further by examining the properties of directly identified VTA GABA neurons, confirming that action potential duration, h current magnitude,

and dopamine D2 receptor response do not distinguish dopamine from GABA VTA neurons [3]. We did observe one major difference: all confirmed dopamine neurons, but no confirmed GABA neurons, were hyperpolarized by GABAB receptor activation [3]. By falsifying a set of long held assumptions these findings have raised the bar for future studies of the functional role of midbrain dopamine neurons in motivation and reinforcement, that Dr. Marisela Morales and I recently summarized in Nature Reviews Neuroscience [4]. With the advent of optogenetic tagging of dopamine neurons, many of our findings in slice have been confirmed using extracellular recording in awake behaving animals, calling into question previous conclusions drawn from recordings of putative dopamine neuron function. It is now standard practice to use more direct methods to identify midbrain neurons, such as Cre driver lines, mRNA analysis, or immunocytochemistry.

1. Margolis EB, Lock H, Hjelmstad GO, Fields HL (2006) The ventral tegmental area revisited: is there an electrophysiological marker for dopaminergic neurons? J Physiol 577, 907-924
2. Margolis EB, Coker AR, Driscoll JR, Lemaitre AI, Fields HL (2010) Reliability in the identification of midbrain dopamine neurons. PLoS One 5, e15222
3. Margolis EB, Toy B, Himmels P, Morales M, Fields HL (2012) Identification of rat ventral tegmental area GABAergic neurons. PLoS One 7, e42365
4. Morales M, Margolis EB (2017) Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nature Reviews Neurosci 18, 73-85

2. VTA neural properties sort by projection target: Given the electrophysiological and pharmacological heterogeneity we observed in the work described above, and the existing anatomical evidence that individual VTA neurons project to only one target, we hypothesized that physiological properties sort by projection target. In 2006 we demonstrated that kappa opioid receptor activation hyperpolarizes prefrontal cortex projecting VTA dopamine neurons, but not nucleus accumbens projecting neurons [5], the first report of a functional property following this organizing principle in VTA dopamine neurons. In this study and the follow-up report, we also showed that action potential duration, h current magnitude, and D2 receptor responses sort by projection target [5,6]. We and other leading neuroscientists studying the VTA have continued to find that a wide variety of physiological properties, anatomical connections, and VTA mediated behaviors sort by projection target (e.g. R. Malenka and E. Nestler). More recently, I have discovered that the distance between the soma and the axon initial segment in VTA neurons also sorts by projection target, regardless of neurotransmitter content, but in parallel to action potential duration [7]. Since our initial observations, the idea that the heterogeneous properties of VTA neurons sort by projection target has become widely accepted and, with the development of optogenetic and chemogenetic methods as well as retrograde viruses, opens new avenues for more penetrating research, furthering our understanding of motivation and reinforcement.

5. Margolis, EB, Lock H, Chefer VI, Shippenberg TS, Hjelmstad GO, Fields HL (2006) Kappa opioids selectively control dopaminergic neurons projecting to the prefrontal cortex. Proc Natl Acad Sci U S A 103, 2938-2942
6. Margolis EB, Mitchell JM, Ishikawa J, Hjelmstad GO, Fields HL (2008) Midbrain dopamine neurons: projection target determines action potential duration and dopamine D(2) receptor inhibition. J Neurosci 28, 8908-8913
7. Margolis EB, Fong PT, Fields HL. The axon initial segment arises from a 'privileged' dendrite at a large and variable distance from the soma in midbrain dopamine neurons. Abstract presented at: Neuroscience 2013; Nov 9-13, San Diego, CA.

3. Opioid control of VTA neurons: Kappa opioid receptor (KOR) activation in the VTA produces conditioned place aversion (CPA) and mu opioid receptor (MOR) activation produces preference (CPP) (e.g. T. Shippenberg). In my graduate work I found that KOR selectively controlled a subset of dopamine neurons [8], and in my postdoctoral work I determined that these are specifically the dopamine neurons that project to the medial prefrontal cortex and amygdala, not the nucleus accumbens [5, 6]. Through a combination of behavioral pharmacology and ex vivo electrophysiology, we found the mechanism by which delta opioid receptors (DORs) in the VTA controls EtOH consumption: DOR inhibition of GABA release onto VTA neurons that develops after the animals commence voluntary EtOH consumption [9]. This effect is protective, preventing the animals from becoming high drinkers [9]. I also collaborated on studies that determined that MOR activation inhibits GABAergic inputs to the VTA from both the nucleus accumbens and the ventral pallidum utilizing optogenetic techniques [10, 11]. In these studies we also found that while ventral pallidal inputs to the VTA make GABAAR synapses onto both dopamine and non-dopamine VTA neurons, the GABAAR synapses from the nucleus accumbens selectively synapse onto non-dopamine neurons, some of which project back to the nucleus accumbens. Together these findings are essential to the ongoing project of determining how exogenous and endogenous opioids produce their motivational actions.

8. Margolis EB, Hjelmstad GO, Bonci A, Fields HL (2003) Kappa-opioid agonists directly inhibit midbrain dopaminergic neurons. J Neurosci 23, 9981-9986
9. Margolis EB, Fields HL, Hjelmstad GP, Mitchell JM (2008) Delta-opioid receptor expression in the ventral tegmental area protects against elevated alcohol consumption. J Neurosci 28, 12672-12681
10. Xia Y, Driscoll JR, Wilbrecht L, Margolis EB, Fields HL, Hjelmstad GO (2011) Nucleus accumbens medium spiny neurons target non-dopaminergic neurons in the ventral tegmental area. J Neurosci 31, 7811-7816
11. Hjelmstad GO, Xia Y, Margolis EB, Fields HL (2013) Opioid modulation of ventral pallidal afferents to ventral tegmental area neurons. J Neurosci 33, 6454-6459

4. Novel signaling pathways of opioid receptors: I have discovered two novel signaling mechanisms for opioid receptors in the VTA. First, I discovered that in stressed animals the DOR activation causes an increase in GABAAR synaptic signaling via rapid insertion of GABAARs into the plasma membrane [12]. This was the first report of a G protein coupled receptor having this effect, and more recently such an effect has been attributed to other receptors such as NPY (T. Kash). I also discovered that the MOR directly excites a subset of VTA neurons by opening a Ca2+ channel (Cav2.1) [13]. This direct excitatory effect occurs at a dose of MOR agonist 2 orders of magnitude lower than the well established presynaptic inhibition of GABA release onto VTA neurons, raising the possibility that this direct excitatory effect dominates unless high concentrations of opioids are present. This excitatory effect also sorts by projection target: VTA neurons that project to infralimbic cortex, but not prelimbic cortex or the nucleus accumbens show this effect [14]. These data, in conjunction with our findings on KOR [5, 6, 8] and presynaptic MOR [10, 11], demonstrate that the opioid receptors are well situated to control multiple selected circuits coursing through the VTA.

12. Margolis EB, Mitchell JM, Hjelmstad GO, Fields HL (2011) A novel opioid receptor-mediated enhancement of GABAA receptor function induced by stress in ventral tegmental area neurons. J Physiol 589, 4229-4242
13. Margolis EB, Hjelmstad GO, Fujita W, Fields HL (2014) Direct bidirectional μ-opioid control of midbrain dopamine neurons. J Neurosci 34, 14707-14716

14. Margolis EB. Rethinking how mu opioid receptors in the ventral tegmental area produce reinforcement: Count the ways. Talk given at: 48th Winter Conference on Brain Research; 2015 January 24-29, Big Sky, MT.